REMARKS/ARGUMENTS

Status of the Claims

Claims 1-4, 10-12, 18, and 21-25 have been canceled without prejudice to or disclaimer of the subject matter encompassed thereby. These claims have been canceled solely to further prosecution. Applicants expressly reserve the right to pursue continuation applications or take other such appropriate measures to seek protection of this canceled subject matter.

Independent claims 5 and 13 have been amended to recite that the composition has a pH of about 3.0 to about 5.0, where the second buffer is selected from the group consisting of glycine, aspartic acid, and sodium succinate. Claim 19 has been rewritten in independent form and amended to recite these same two claim limitations. Claim 20 accordingly been amended to depend from claim 19. Support for the pH limitation for these compositions resides in the specification, for example, at page 15, lines 15-18; support for these preferred buffers resides in the specification, for example, at page 15, lines 15-18. No new matter has been added by way of claim amendment.

New claims 36-49 have been added. Claims 36 and 37 are directed to specific embodiments of independent claims 5 and 13, respectively, wherein the first buffer is selected from the group consisting of glucine, aspartic acid, and sodium succinate. Support for these claims resides in the specification, for example, at page 15, lines 1-2. New claims 38-41 and 46-49 are directed to specific embodiments of claim 19 and new claim 42, respectively. Support for these claims resides throughout the specification, for example, at page 6, line 27, continuing through page 7, line 16 (claim 38); at page 6, lines 23-26 (claim 39); at page 10, line 18, continuing through page 11, line 4 (claim 39); and at page 8, lines 16-19, and page 9, lines 4-7 (claim 41). New claim 42 is directed to a pharmaceutical composition comprising IFN-β, wherein the first buffer and the second buffer recited in the formulation steps are selected from the group consisting of glycine, aspartic acid, and sodium succinate. Support for this claim resides in the specification, for example, at page 15, lines 1-18. New claims 43, 44, and 45 are specific embodiments of claim 42, wherein the composition comprises substantially monomeric IFN-β (claim 43), and is prepared using glycine as the first buffer (claim 44), and aspartic acid as

the second buffer (claim 45). Support for these claims resides throughout the specification, for example, at page 4, lines 1-9, and at page 15, lines 1-18. No new matter is added by way of presentation of new claims.

Applicants acknowledge that the election is treated as an election without traverse. For the record, Applicants' intent was to elect the Group II claims without traverse, as evidenced by the Preliminary Amendment filed concurrently with the Response to the Restriction Requirement. The claim amendments presented in that Preliminary Amendment were made solely as a result of the election of the Group II invention for prosecution in the present application. Further, Applicants have filed a divisional application (assigned U.S. Application Serial No. 10/750,076, filed December 31, 2003) to seek protection of the methods recited in the claims of the non-elected Group I invention.

Applicants also take this opportunity to draw the attention of the Examiner to copending and commonly owned U.S. Patent Application No. 10/035,397, filed October 25, 2001.

Claims 1-35 are now pending in the application. Reexamination and reconsideration of the claims is respectfully requested in view of these amendments and the following remarks. The Examiner's comments are addressed below in the order set forth in the Office Action.

Objections to the Specification

The Office Action objects to a blank space on page 1, line 33. Applicants respectfully note that the blank space resides on line 3 of page 1. Applicants have amended the specification to provide the application number of the priority document referenced on line 3 of page 1. Accordingly, this objection to the specification is overcome.

The Rejection of the Claims Under 35 U.S.C. §102(b) Should Be Withdrawn

Claims 1, 2, 14-18, and 20-35 are rejected under 35 U.S.C. §102(b) in light of Dorin *et al.*, U.S. Patent 5,814,485 (hereinafter the "Dorin *et al.* patent"). Claims 1, 2, 18, and 21-25 have been canceled to further prosecution. This rejection is respectfully traversed with regard to the remaining claims.

Applicants agree that a method of manufacture cannot confer novelty "if the product is the same as ...a product of the prior art" (*In re Thorpe* 777 F.2d 695 at 698 (Fed. Cir. 1985) *as cited in* the Office Action mailed February 20, 2004). However, Applicants respectfully note that the presently claimed interferon-beta (IFN-β) containing compositions are not "the same as ...a product in the prior art." The products in the pending claims are compositions comprising IFN-β and which have a pH of about 3.0 to about 5.0.

In contrast, Dorin *et al.* teach methods of recombinant production of IFN-β and its subsequent purification, and disclose various excipients that can be included in IFN-β formulations having a pH of about 6.0 to 7.5 (for pH and suitable buffers, see the specification at col. 13, lines 44-54). Applicants respectfully note that the monomeric state of the IFN-β in the formulations prophetically disclosed in this cited patent is not addressed by Dorin *et al.* Rather, the statement regarding monomeric state is made in the context of the protein purification process. Notably, the specification of this cited patent teaches that "...the [IFN-β] polypeptide will be solubilized and reduced to monomer form before [emphasis added] oxidation and refolding." *Id.* at column 10, lines 5-9. The degree to which the oxidized and refolded protein remains in its monomeric state in a pharmaceutical composition depends upon the oxidation, refolding, and formulation processes.

In view of these remarks, Applicants respectfully submit that the Dorin *et al.* patent teaches IFN-β compositions having a pH that is outside the range of the pH of the presently claimed IFN-β compositions. Accordingly, as the cited reference does not teach each and every limitation of the claimed compositions, Applicants respectfully submit that this rejection of the claims should be withdrawn and should not be applied to the new claims.

The Rejection of the Claims Under 35 U.S.C. §103 Should Be Withdrawn

Claims 3 and 19 are rejected under 35 U.S.C. §103 over U.S. Patent No. 5,814,485 (hereinafter the "Dorin *et al.* patent") in view of U.S. Patent No. 5,183,746 (hereinafter the "Shaked *et al.* patent"). Claim 3 has been canceled to further prosecution. This rejection is respectfully traversed as applied to claim 19.

Claim 19 is directed to a composition having a pH of about 3.0 to about 5.0 and which comprises substantially monomeric IFN-β. The composition has been prepared by mixing a sample comprising substantially purified IFN-β with guanidine HCl, renaturing the resulting solubilized denatured protein with a glycine, aspartic acid, or sodium succinate buffer having a pH of about 3.0 to about 5.0. Thus, the presently claimed composition comprises substantially monomeric IFN-β in a glycine, aspartic acid, or sodium succinate buffer at a pH of about 3.0 to about 5.0.

In contrast, the IFN-β compositions disclosed in the Dorin *et al.* patent are formulated with a buffer having a pH of about 6.0 to 7.5. Suitable buffers include sodium citrate or phosphate. There is no suggestion to formulate these compositions within a low pH range; to the contrary, this cited reference teaches away from this pH range, noting:

> Maintenance of pH is critical to prevent such physical and chemical alterations, such as oxidation, during storage of the IFN-β polypeptide. The pH will be chosen not only to optimize the longevity of the IFN-β polypeptide but to ease administration of the IFN-β polypeptide to humans. Usually, the pH of the formulation is adjusted to between 6.0 and 7.5 with NaOH if a sodium containing buffering reagent is used. More preferably the pH is adjusted to 6.5.

See, Dorin *et al.*, col. 13, lines 46-54.

The Office Action cites to the Shaked *et al.* patent as teaching that low pH can be used to formulate IFN-β and therefore provides a motivation to combine these two references, and modify the teachings therein, to arrive at Applicants' claimed invention. Applicants respectfully disagree.

The Shaked *et al.* patent teaches liquid or lyophilized formulations of IFN-β dissolved in an inert carrier medium comprising one or more biocompatible non-ionic polymeric detergents, or the combination of one or more non-ionic biocompatible polymeric detergents with an additional solubilizing/stabilizing agent, where suitable additional solubilizing/stabilizing agents include SDS and glycerol. See, for example, the Abstract; the Summary at col. 5, lines 21-30; and the Detailed Description at col. 7, lines 37-45. The liquid IFN-β compositions comprise a

buffer that maintains the formulation at "a physiologically acceptable pH range" (col. 13, lines 11-18). The lyophilized IFN-β compositions comprise a buffer that maintains the formulation at "a physiologically acceptable pH range upon reconstitution" and further comprise a carrier (col. 14, lines 40-47). The specification further states that the pharmaceutical compositions constitute "an aqueous solution of IFN-β protein at pH 3.5 to 9.5 . . . still more preferably about pH 6, from which the protein will not precipitate" (col. 8, lines 55-59). Thus, even Shaked *et al.* would lead one of skill in the art to formulate IFN-β compositions at the preferred more neutral pH range disclosed in their patent specification as about pH 6.0 to about 8.5 (col. 8, lines 45-47).

Even if one of skill in the art were motivated to combine the teachings of the Shaked *et al.* patent with the teachings of the Dorin *et al.* patent, there would be no reasonable expectation of their successfully arriving at Applicants' claimed invention. Neither of these cited patents teach that IFN-β should or even could be formulated at low pH using a glycine, aspartic acid, or sodium succinate buffer.

Dorin *et al.* limits their buffer disclosure to sodium citrate or phosphate, as noted above. The only disclosure within the Shaked *et al.* patent of specific buffers suitable for formulating the IFN-β compositions disclosed therein resides at col. 15, lines 18-23, stating "[f]or lyophilized formulations, the buffer is preferably selected from buffers, such as citrate, maleate, acetate and phosphate, more preferably acetate or phosphate, and still more Preferably [*sic*] phosphate." All of the specific IFN-β formulations set forth in the experimental examples of the Shaked *et al.* patent are prepared using the two basic processes outlined as Scheme 1A and 1B (tables at col. 21 and 22) and Scheme 2A and 2B (tables at col. 22 and 23). The final stages of these formulation processes include a desalting step with a transfer component (sodium laurate) in sodium phosphate buffer or Tris-HCL, pH 9.2, rapid lowering of pH to 3.0 with 1.0 N HCL to precipitate the transfer component, subsequent formulation with the stabilizer/solubilizer, and neutralization to higher pH, usually pH 5.0 to 7.0, with NaOH. The Shaked *et al.* patent makes no suggestion of formulating low pH IFN-β compositions using a glycine, aspartic acid, or sodium succinate buffer. This missing claim limitation is also not taught or suggested by Dorin *et al.*

In summary, the combined disclosures of these two cited references fail to teach or even suggest the composition recited in claim 19. Accordingly, this rejection of claim 19 should be withdrawn, and should not be applied to the new claims.

New Claims Presented

New claims 36-49 are directed to narrow embodiments of claims 5, 13, and 19. All of these compositions have a pH of about 3.0 to about 5.0, and therefore are not anticipated by the Dorin *et al.* reference. Furthermore, they are all formulated with a buffer that is selected from the group consisting of glycine, aspartic acid, and sodium succinate. IFN-β formulations comprising glycine, aspartic acid, or sodium succinate buffer and having a pH of about 3.0 to about 5.0 are not taught or suggested by the Dorin *et al.* and Shaked *et al.* patent, either alone or in combination. Accordingly, these new claims are novel and nonobvious in view of the art cited herein.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the objection to the specification and the rejections of the claims under 35 U.S.C. §102(b) and 35 U.S.C. §103 are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of

this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Leslie T. Henry
Registration No. 45,714

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

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Lynda-Jo Pixley